REMARKS

I. Status of the Claims

Claims 17-23 are pending in the application. Claims 17-22 have been withdrawn pursuant to a restriction requirement and are canceled herein. Claim 23 has been examined and stands rejected. The specific grounds of rejection, and applicants' responses thereto, are set out in detail below.

II. Restriction Requirement.

Pursuant to an oral restriction requirement, and an oral response thereto, claim 23 (Group II) has been elected for prosecution herein. Applicants hereby affirm the election of claim 23 (Group II).

III. Formalities

The examiner has requested an amendment to page 2 of the specification, updating priority information. An appropriate amendment has been provided.

The examiner also has objected to the abstract. A new abstract has been provided.

IV. Rejection Under 35 U.S.C. §112, First Paragraph

Claim 23 stands rejected as lacking an enabling disclosure in the specification. According to the examiner, the specification is defective in (a) failing to provide an adequate basis for predicting that increasing α-MHC transcripts would benefit subjects having myocardial failure, (b) failing to provide correlation of α-MHC transgene expression *in vivo* with therapeutic

benefit, and (c) failing to teach or provide guidance with respect to specific levels of α-MHC that would be therapeutic. Applicants respectfully traverse.

First, applicants submit that the examiner is incorrect in arguing that there is insufficient evidence of increased α-MHC expression leading to patient benefit. However, applicants provide a recent publication, and the accompanying declaration, as additional proof.[1] The relied upon study examined MHC expression as a function of improved disease-state phenotype. This study showed a direct correlation between α- and β-MHC levels and a diseased heart state. Importantly, the age variation in the study subjects was minimal: 54.1 $\pm$ 10.5 years for tests and 49.1 $\pm$ 4.6 years for controls. Thus, the study was able to isolate the disease state as a variable and eliminate age as a complicating factor. The results, as attested to in the accompanying declaration, provide clear evidence that there is a direct, predictable and statistically relevant correlation between levels of α- and β-MHC and myocardial failure.

Second, it also is disputed that there is insufficient evidence that therapeutic benefit can be achieved *in vivo*. The above referenced study used β-adrenergic blocking agents to improve the systolic function of subjects who exhibited the idiopathic dilated cardiomyopathy phenotype. The study measured expression levels of several genes and found a direct correlation with improvement in left ventricular ejection fraction (LVEF - an effective measure of systolic contractile dysfunction) and levels of α- and β-MHC. Specifically, as LVEF improved following treatment with β-adrenergic blocking agents, mRNA levels of α-MHC increased and mRNA levels of β-MHC levels decreased. This showing clearly only refutes the examiner's position regarding *in vivo* efficacy.

[1] It is noteworthy that the §112 rejection in the companion '733 application was withdrawn in the face of this very evidence.

With regard to both of these points, it also should be noted that monitoring gene expression levels in an intact heart ***as the phenotype is modified*** leads to more direct assessment of potential correlating factors that might exist. In addition, due to the combinatorial nature of gene expression, measuring gene expression levels from an intact heart allows one to view data in the presence of the net regulatory influences. For these reasons, the present study provides data that is very reliable in terms of how gene expression levels relate to myocardial failure. Using these preferred experimental conditions, the present study shows a clear correlation between α- and β-MHC levels and the diseased state of the heart.

Third, the examiner argues that the amount of expression needed to achieve clinical benefit is not established. This statement is not understood. The application and the study above both provide baselines for normal and abnormal MHC expression. Moreover, the ability to track the elevation of α-MHC levels during the course of treatment provides a "real time" assessment of α-MHC levels as cardiac output improved. Thus, one can very readily determine at what point therapeutic efficacy is achieved. It also is not relevant that "complete amelioration" would be encompassed by therapy. The question is whether "therapy" is supported, and the numerous embodiments short of "complete amelioration" would be sufficient for this.

Finally, the examiner argues that gene therapy for cardiac tissue is complicated, unproven, and hence unpredictable. In support, a number of general references regarding gene therapy are advanced. However, applicants submit that cardiac gene therapy, though admittedly complicated, is not *per se* nonenabled. A number of publications, far more relevant than those cited by the examiner, report on the successful transfer of genes into cardiac tissue. Alexander *et al.*, *Clin. Exp. Pharmacol. Physiol.*, 26:661-668 (1999) reported gene transfer into myocardium through direct injection of plasmid DNA and viral transfer. Chien *et al.*, WO/2000/15821

describe the use of recombinant adenovirus-mediated expression of transgenes in both neonatal and mature cardiac tissues. Other papers reporting cardiac transgene expression included Davidson *et al.*, *Circulation* 104:131 (2001), Pachucki *et al.*, *Endocrinology* 142:13 (2001), Shinmura *et al.*, *Japan Heart J.* 41:633 (200), Silva *et al.*, *FASEB* 14:1858 (2000), Lenhart *et al.*, *Am. J. Physiol. Heart Circ. Physiol.* 279:H986 (2000), Lazarous *et al.*, *Cardiovasc. Res.* 44:294 (1999), and Wickenden *et al.*, *Circ. Res.* 85:1067 (1999). Thus, applicants respectfully submit that there is a sufficient basis for gene therapy in cardiac tissue.

In short, applicants submit that the present application provides adequate evidence of the value of α-MHC therapy. In addition, the use of gene therapy in cardiac tissue is not so far beyond the realm of possibility that it is non-enabled. Reconsideration and withdrawal is respectfully requested.

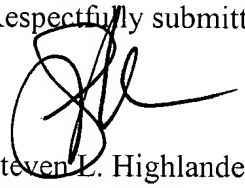
V. Rejection Under 35 U.S.C. §112, Second Paragraph

Claim 23 is rejected under the second paragraph of §112 as indefinite. Applicants have provided an amendment to claim 23 that is believed to address the examiner's concerns. Reconsideration and withdrawal of the rejection is respectfully requested.

VI. Conclusion

In light of the foregoing, applicants respectfully submit that all claims are in condition for allowance, and an early notification to that effect is earnestly solicited. Should Examiner Ton have any questions regarding this response, a telephone call to the undersigned is invited.

Respectfully submitted,



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APPENDIX A1: MARKED UP COPY OF SPECIFICATION

23. (Amended) A method of treating myocardial failure in a human comprising administering an effective amount of [The method of Claim 17 wherein the agent is] a transgene encoding for α-MHC.

APPENDIX A2: MARKED UP COPY OF CLAIMS

Page 1, lines 3-5:

Benefit of provisional applications 60/036,987, filed January 30, 1997, and 60/038,911, filed February 26, 1997, and U.S. Serial No. 09/415,733, filed October 12, 1999, is hereby claimed.

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[INSERT]

A correlation between increased β-myosin heavy chain and decreased α-myosin heavy chain (MHC) expression and cardiac hypertrophy is established herein. The change in expression levels of these molecules can therefore be used to diagnosis hypertrophic conditions. In addition, by modulating the levels of α- and β-MHC towards their norm, one can provide therapies for cardiac hypertrophy, and thus limit progression to cardiac dysfunction.